Pediatric Formulations

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Outline

1. Marketed Pediatric Dosage Forms
2. Formulation Considerations for Marketing
3. Compounding of Marketed Drug Products
4. Conclusion

MARKETED PEDIATRIC DOSAGE FORMS

Types of Oral Dosage Forms

- Liquid Dosage Forms
- Solids for Reconstitution as a Suspension or Solution
- Solid Dosage Forms

Marketed Pediatric Dosage Forms

- Solution/Syrups/Elixir
- Suspension
- Powders for Reconstitution as Suspension
- Dispersible/Effervescent Tablets
- Chewable Tablets
- Orally Disintegrating Tablets
- Tablets/Coated Tablets
- Sprinkle Oral Powder or Granules
- Capsules

Preferred Dosage Forms for Drug Delivery to Different Pediatric Age Groups

Neonates: 0-4 weeks	???
Infants: 1 month-2 year	Liquids-small volumes (syrups, solutions)
Children: 2-5 years	**Liquids (Liquids and effervescent tablets dispersed in liquids for administration)**
Children: 6-11 years	**Solids (Chewable tablets, orally disintegrating tablets)**
Adolescents: 12-18 years	Solids (typical adult dosage forms –tablets, capsules)

6 years old is generally considered the age that children can safely swallow a solid oral dosage form, although this varies based on the child

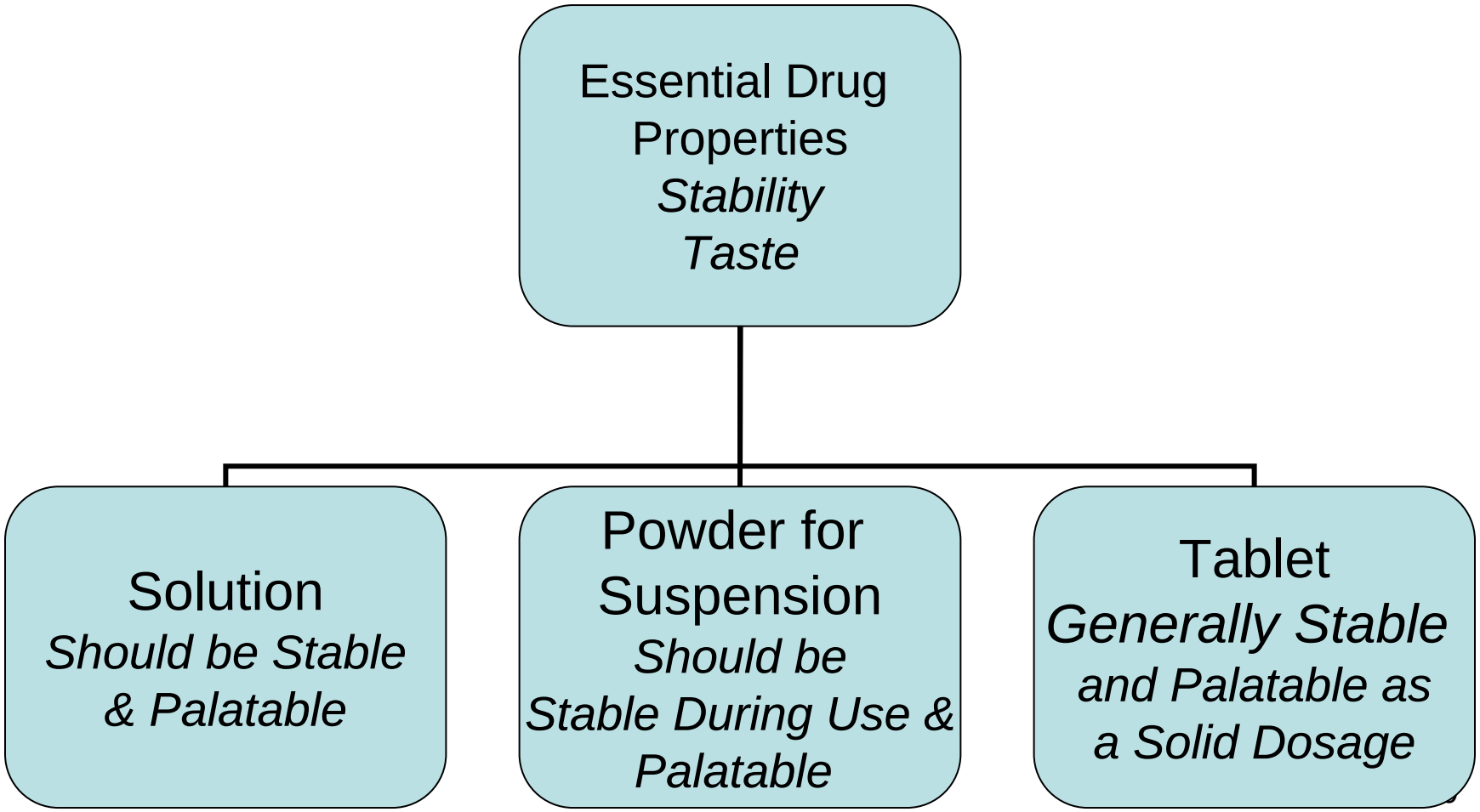
Approved Oncology Dosage Forms

- Injections 71
- Tablets 24
- Capsules 15
- Topical 5
- Total 115

Note: Considerable number of drugs approved are orally active

FORMULATION CONSIDERATIONS

Rationale for Formulation Design



Concern for Potential Changes upon Storage in Formulation Design

- **Solution**

  precipitation

  discoloration
- **Powder for Oral Suspension**

  caking - difficulty in dispersing the powder upon reconstitution
- **Tablet**

  chewable tablet hardening

FDA Expectations for Liquid Formulations

- Palatability (taste, texture, smell)
- Chemical Stability of Ready to Use Solutions or Suspensions
- Physical Stability of Suspensions
- Proper Measuring Device
- Suitable Container/Closures
- Excipients (safety consideration)

Advantages of a Liquid Dosage Form for Pediatrics

- Most desirable dosage form up to age up to 6 years and beyond
- Ease of administration
- Accuracy in dosing (critical in chemotherapy)
- Physical & Chemical properties (solubility, stability, taste, etc.) established during early development
- Compatibility with excipients for liquid formulation can be screened more rapidly
- Depending on the drug properties, a solution or suspension can be developed

FDA Expectations for Oral Solid Dosage Forms for Pediatrics

- Ease in swallowing
- Palatability
- Dosing accuracy
- Suitable package for good compliance
- Clear identification when several strengths of the same product are presented

Issues with Oral Solid Dosage Forms for Pediatrics

Manufacturing

- Dosing uniformity with very low doses
- Tablet size and shape/capsule size
- Scored tablets

Controls

- Disintegration/dissolution
- Impurities/degradation products justification

Dosing Accuracy Achieved with Very Low Doses Using Scored or Un-scored Tablets

- Children weighing <20 Kg
- Dosage forms: Scored tablet & Un-scored tablet
- Dosing: Twice a day

Weight band	Scored tablet	Un-Scored tablet
14< 20 kg	*2.5 tablet am and pm*	*3 tablets in am & 2 in pm*

COMPOUNDING OF MARKETED DRUG PRODUCT

Compounding of Marketed Drug Product

- Compounding of marketed product as per label
- Extemporaneous Formulation - Compounding of marketed product not approved in the label

Compounding of Marketed Product as per Label

Pharmacies can prepare oral liquid dosage forms from commercially available solid tablets and capsules

J Pharm Sci. 2008 May;97(5):1731-74.

Extemporaneous Formulations NOT Approved in the Label

- Extemporaneous Formulations prepared by a pharmacist from an approved drug product based on the information provided in the literature.

Limitations in Developing Extemporaneous Formulations Not Approved in the Label

- Lack of stability/sterility studies
- Lack of PK/PD/bioavailability studies
- Efficacy and safety concerns
- Adverse-event reporting
- Variations in practice
- Poor coordination and sharing of information

Clin Ther. 2008; 30:2112-2119.

Compounding of Oncology Formulation Approved in the Label

Gleevec: 100 mg and 400 mg tablet

Glevec can be dissolved in water and apple juice for patients having difficulty in swallowing

Extemporaneous Oncology Formulation Not Approved in the Label

Etoposide

Marketed Drug product: Injection - 20 mg/mL

Literature: Oral Solution

- Dilute 1:1 with Normal Saline
- Storage Conditions: Room Temperature
- Expiration Date: 22 days

Excipients with Elevated Toxicological Risk for Preterm and Term Neonates and Infants <6 months

Excipient	Administration	Adverse reaction
Benzyl alcohol	Oral, parenteral	Neurotoxicity, metabolic acidosis
Ethanol	Oral, parenteral	Neurotoxicity
Polyethylene glycol	Parenteral	Metabolic acidosis
Polysorbate 20 Polysorbate 80	Parenteral	Liver & kidney failure
Propylene glycol	Oral, parenteral	Seizures, neurotoxicity, hyperosmolarity

CONCLUSION

What are the Advantages of Marketed Dosage Forms and Compounded as per Label?

- Drug product safety information with respect to degradation products and excipients are established.
- Drug product quality information with respect to shelf life, palatability and accurate dosing devises are also established.
- Although, extemporaneous formulations serve a useful purpose in early oncology studies, a preferred approach would be to develop “To be marketed product.”

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THANK YOU!